

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:42887 CAPLUS
DOCUMENT NUMBER: 137:24295
TITLE: Salts of an isothiazole-4-carboxamide derivative,
namely 3-(4-bromo-2,6-difluorobenzoyloxy)-5-[3-(4-

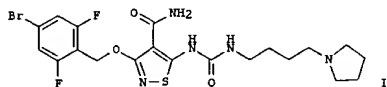
pyrrolidin-1-ylbutyl)ureido]isothiazole-4-carboxylic
acid amide, and their use as

anti-hyperproliferation

agents
INVENTOR(S): Gant, Thomas G.; Williams, Glenn Robert
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002044158	A1	20020606	WO 2001-1B2193	20011119
V: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CH, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.: US 2000-253513P P 20001128				

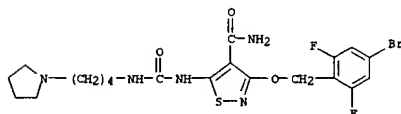


AB The invention relates to the hydrochloride, hydrobromide, hemi-citrate, acetate, p-tosylate, L-tartrate, hemi-succinate, and mesylate salt forms of 3-(4-bromo-2,6-difluoro-benzoyloxy)-5-[3-(4-pyrrolidin-1-

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)
RN 252003-66-0 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monomethanesulfonate (9CI)
(CA INDEX NAME)

CH 1

CRN 252003-65-9
CMF C20 H24 Br F2 N5 O3 S



CH 2

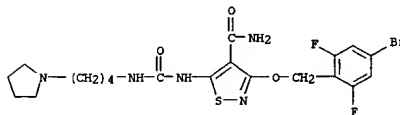
CRN 75-75-2
CMF C H4 O3 S



RN 252003-71-7 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monohydrochloride (9CI)
(CA INDEX NAME)

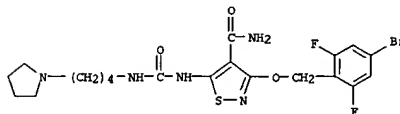
L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)
ylbutyl)ureido]isothiazole-4-carboxylic acid amide (I). These salts of I are useful in the treatment of various hyperproliferative diseases, including cancers (no data). The invention also relates to pharmaceutical compns. contg. these salts. The invention further relates to methods of treating hyperproliferative diseases, such as cancers, in mammals, esp. humans, by administering the above salts, and to methods of prep. the crystal forms of the salts. For instance, I was dissolved in refluxing EtOH, and the soln. was cooled to ambient temp., treated with 1 equiv HCl (1.0M in Et2O), heated to 50.degree., and cooled at room temp. for 3 days to give I.HCl in 82% yield. The advantageous properties of all the salts are described in detail; e.g., I.HCl showed high crystallinity, was hygroscopically stable, and had a low tendency for concd. aq. solns. to form viscous mixts. on standing. Characterizing X-ray powder diffraction spectra are given for I and salts, both as tables and graphical figures.
IT 252003-66-0P, 3-[(4-Bromo-2,6-difluorobenzoyloxy)-5-[3-(4-(pyrrolidin-1-yl)butyl)ureido]isothiazole-4-carboxylic acid amide mesylate
252003-71-7P, 3-[(4-Bromo-2,6-difluorobenzoyloxy)-5-[3-(4-(pyrrolidin-1-yl)butyl)ureido]isothiazole-4-carboxylic acid amide hydrochloride (1:1) 433978-97-3P, 3-[(4-Bromo-2,6-difluorobenzoyloxy)-5-[3-(4-(pyrrolidin-1-yl)butyl)ureido]isothiazole-4-carboxylic acid amide hydrobromide (1:1) 433978-98-4P, 3-[(4-Bromo-2,6-difluorobenzoyloxy)-5-[3-(4-(pyrrolidin-1-yl)butyl)ureido]isothiazole-4-carboxylic acid amide hemicitrate 433978-99-5P, 3-[(4-Bromo-2,6-difluorobenzoyloxy)-5-[3-(4-(pyrrolidin-1-yl)butyl)ureido]isothiazole-4-carboxylic acid amide acetate 433979-00-1P, 3-[(4-Bromo-2,6-difluorobenzoyloxy)-5-[3-(4-(pyrrolidin-1-yl)butyl)ureido]isothiazole-4-carboxylic acid amide p-tosylate 433979-01-2P, 3-[(4-Bromo-2,6-difluorobenzoyloxy)-5-[3-(4-(pyrrolidin-1-yl)butyl)ureido]isothiazole-4-carboxylic acid amide L-tartrate 433979-02-3P, 3-[(4-Bromo-2,6-difluorobenzoyloxy)-5-[3-(4-(pyrrolidin-1-yl)butyl)ureido]isothiazole-4-carboxylic acid amide hemisuccinate
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and X-ray powder diffraction spectra of pharmaceutical salts of (bromodifluorobenzoyloxy) [(pyrrolidinylbutyl)ureido]isothiazolecarboxamide for use as antihyperproliferatives)

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)



● HCl

RN 433978-97-3 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monohydrobromide (9CI)
(CA INDEX NAME)



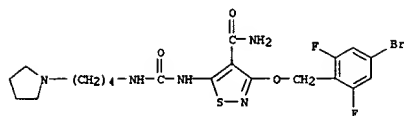
● HBr

RN 433978-98-4 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1) (9CI) (CA INDEX NAME)

CH 1

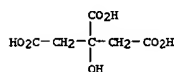
CRN 252003-65-9
CMF C20 H24 Br F2 N5 O3 S

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)



CH 2

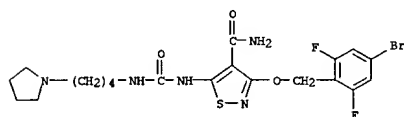
CRN 77-92-9
CHF C6 H8 O7



RN 433978-99-5 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino-, monoacetate (9CI) (CA INDEX NAME)

CH 1

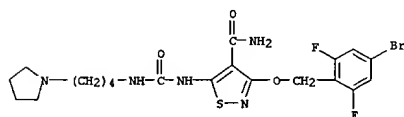
CRN 252003-65-9
CHF C20 H24 Br F2 N5 O3 S



CH 2

CRN 64-19-7
CHF C2 H4 O2

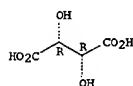
L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)



CH 2

CRN 87-69-4
CHF C4 H6 O6

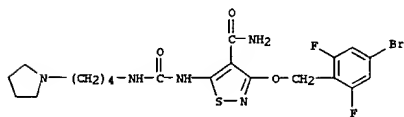
Absolute stereochemistry.



RN 433979-02-3 CAPLUS
CN Butanedioic acid, compd. with
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-
[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-4-isothiazolecarboxamide
(1:2) (9CI) (CA INDEX NAME)

CH 1

CRN 252003-65-9
CHF C20 H24 Br F2 N5 O3 S



CH 2

CRN 110-15-6
CHF C4 H6 O4

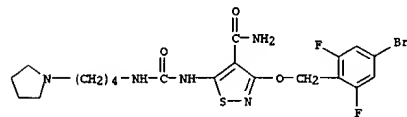
L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)



RN 433979-00-1 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino-, mono(4-methylbenzenesulfonate) (9CI) (CA INDEX NAME)

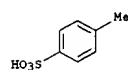
CH 1

CRN 252003-65-9
CHF C20 H24 Br F2 N5 O3 S



CH 2

CRN 104-15-4
CHF C7 H8 O3 S

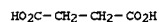


RN 433979-01-2 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CH 1

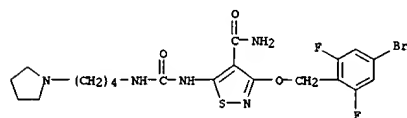
CRN 252003-65-9
CHF C20 H24 Br F2 N5 O3 S

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)



IT 252003-65-9, 3-[(4-Bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-yl)butyl]ureido]isothiazole-4-carboxylic acid amide
RL: FRP (Properties); RCT (Reactant); RACT (Reactant or reagent)
(prepn. and X-ray powder diffraction spectra of pharmaceutical salts of

(bromodifluorobenzyl)oxy [(pyrrolidinylbutyl)ureido]isothiazolecarboxamide for use as antihyperproliferatives)
RN 252003-65-9 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino- (9CI) (CA INDEX NAME)

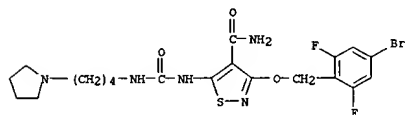


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:784087 CAPLUS
DOCUMENT NUMBER: 132:22961
TITLE: Preparation of isothiazolamide urea derivatives
as
INVENTOR(S): anticancer agents
Larson, Eric Robert; Noe, Mark Carl; Gant, Thomas
George
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 132 pp.
CODEN: FIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9962890	A1	19991209	WO 1999-1B797	19990503
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,			
DE,	DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP,			
KE,	KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,			
MW,	MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,			
TR,	TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU,			
TJ, TM	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE,			
DK,	ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,			
CG,	CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
AU 9933421	A1	19991220	AU 1999-33421	19990503
BR 9910900	A	20010213	BR 1999-10900	19990503
EP 1084114	A	20010321	EP 1999-914724	19990503
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT,			
IE,	SI, LT, LV, FI, RO			
JP 2002517384	T2	20020618	JP 2000-552102	19990503
US 6235764	B1	19991220	US 1999-316837	19990521
ZA 9903752	A	20001204	ZA 1999-3752	19990603
NO 200006071	A	20001130	NO 2000-6071	20001130
US 2001020034	A1	20010906	US 2001-803296	20010309
PRIORITY APPLN. INFO.:			US 1998-87963P P 19980604	
			WO 1999-1B797 W 19990503	
			US 1999-316837 A3 19990521	
OTHER SOURCE(S):	MARPAT 132:22961			
GI				

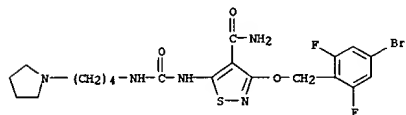
L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)



RN 252003-66-0 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monomethanesulfonate
(9CI)
(CA INDEX NAME)

CM 1

CRN 252003-65-9
CMF C20 H24 Br F2 N5 O3 S



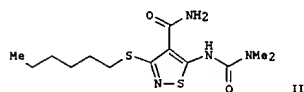
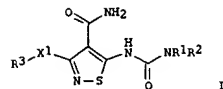
CM 2

CRN 75-75-2
CMF C H4 O3 S



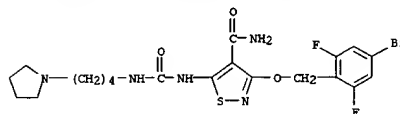
RN 252003-71-7 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monohydrochloride
(9CI)
(CA INDEX NAME)

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)



AB Title compds. (I) [X1 = O or S; R1 = H, (un)substituted alkyl, alkenyl, alkynyl, acyl, (CH2)t(hetero)aryl, C(O)(CH2)t(hetero)aryl, etc.; t = 0-5; R2 = R1, SO2(CH2)t(hetero)aryl, etc.; or R1 and R2 taken together with the attached N = 4-10 membered (un)substituted poly- or monocyclic ring or 5-10 membered (un)substituted heteroaryl ring; R3 = H, (un)substituted alkyl, alkenyl, alkynyl, (CH2)t(hetero)aryl, etc.] were prepd. for use in the treatment of hyperproliferative disorders, such as cancer. Thus, 3-(4-cyano-3-mercaptoisothiazol-5-yl)-1,1-dimethylurea (prepn. given) was alkylated with 1-iodohexane (51%) and the product treated with concd. H2SO4 to yield the isothiazolamide (II) (78%). I are inhibitors of receptor tyrosine kinases and bind to or modulate the KDR/FLK-1 receptor (no data) and may be used to treat disorders related to vasculogenesis or angiogenesis.
IT 252003-65-9P 252003-66-0P 252003-71-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (target compd.; prepn. of isothiazolamide urea derivs. as anticancer agents and for the treatment of disorders related to vasculogenesis and/or angiogenesis)
RN 252003-65-9 CAPLUS
CN 4-Isouthiazolecarboxamide,
3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]- (9CI) (CA INDEX NAME)

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS (Continued)



● HCl

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	9.17	224.82
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-1.24	-1.24

STN INTERNATIONAL LOGOFF AT 17:36:07 ON 20 SEP 2002

Connecting via Winsock to STN

Welcome to STN International! Enter x:X

LOGINID:sssptal626amd

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2	Apr 08	"Ask CAS" for self-help around the clock
NEWS	3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS	4	Apr 09	ZDB will be removed from STN
NEWS	5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS	6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS	7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS	8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS	9	Jun 03	New e-mail delivery for search results now available
NEWS	10	Jun 10	MEDLINE Reload
NEWS	11	Jun 10	PCTFULL has been reloaded
NEWS	12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS	13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS	14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS	15	Jul 30	NETFIRST to be removed from STN
NEWS	16	Aug 08	CANCERLIT reload
NEWS	17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS	18	Aug 08	NTIS has been reloaded and enhanced
NEWS	19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS	20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS	21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS	22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS	23	Sep 03	JAPIO has been reloaded and enhanced
NEWS	24	Sep 16	Experimental properties added to the REGISTRY file
NEWS	25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS	26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS	EXPRESS		February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS	HOURS		STN Operating Hours Plus Help Desk Availability
NEWS	INTER		General Internet Information
NEWS	LOGIN		Welcome Banner and News Items
NEWS	PHONE		Direct Dial and Telecommunication Network Access to STN
NEWS	WWW		CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer

agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 17:33:24 ON 20 SEP 2002

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 17:33:37 ON 20 SEP 2002

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2002 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 19 SEP 2002 HIGHEST RN 453507-55-6

DICTIONARY FILE UPDATES: 19 SEP 2002 HIGHEST RN 453507-55-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>

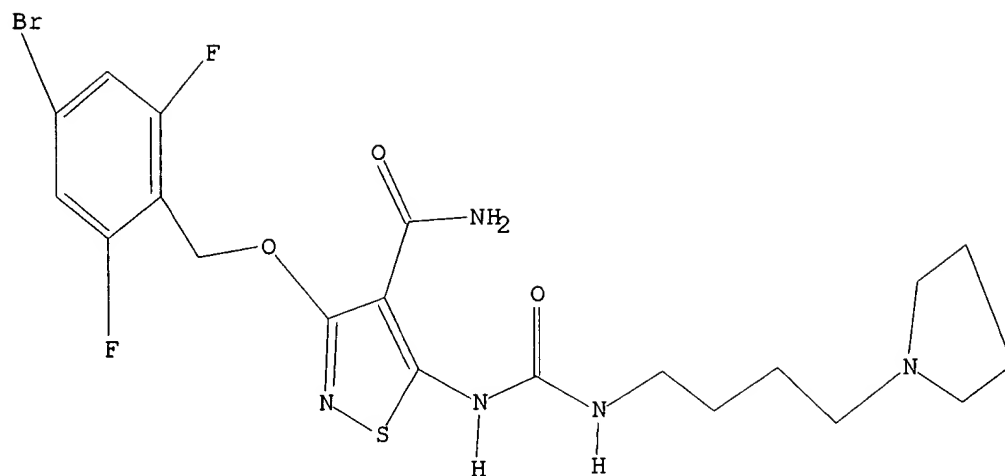
Uploading 0993640.str

L1 STRUCTURE UPLOADED

=> d

L1 HAS NO ANSWERS

L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1 ful

FULL SEARCH INITIATED 17:33:54 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 43 TO ITERATE

100.0% PROCESSED 43 ITERATIONS

10 ANSWERS

SEARCH TIME: 00.00.01

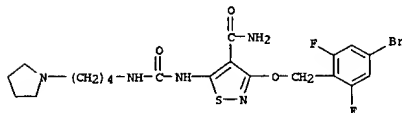
L2 10 SEA SSS FUL L1

=> d 1-10

L2 ANSWER 1 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 433979-02-3 REGISTRY
 CN Butanedioic acid, compd. with
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-
 {[(4-(1-pyrrolidinyl)butyl)amino]carbonyl}amino-4-isothiazolecarboxamide
 (1:2) (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(4-bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-
 yl)butyl]ureido]isothiazole-4-carboxylic acid amide hemisuccinate
 MF C20 H24 Br F2 N5 O3 S . 1/2 C4 H6 O4
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER

CH 1

CRN 252003-65-9
 CMF C20 H24 Br F2 N5 O3 S



CH 2

CRN 110-15-6
 CMF C4 H6 O4

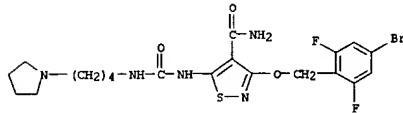
HO₂C-CH₂-CH₂-CO₂H

1 REFERENCES IN FILE CA (1962 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L2 ANSWER 2 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 433979-01-2 REGISTRY
 CN 4-isothiazolecarboxamide,
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(4-bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-
 yl)butyl]ureido]isothiazole-4-carboxylic acid amide L-tartrate
 FS STEREORESEARCH
 MF C20 H24 Br F2 N5 O3 S . C4 H6 O6
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER

CH 1

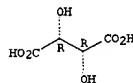
CRN 252003-65-9
 CMF C20 H24 Br F2 N5 O3 S



CH 2

CRN 87-69-4
 CMF C4 H6 O6

Absolute stereochemistry.

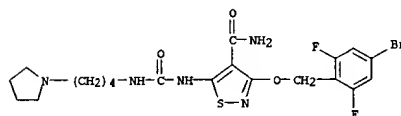


1 REFERENCES IN FILE CA (1962 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L2 ANSWER 3 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 433979-00-1 REGISTRY
 CN 4-isothiazolecarboxamide,
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, mono(4-methylbenzenesulfonate) (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(4-bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-
 yl)butyl]ureido]isothiazole-4-carboxylic acid amide p-tosylate
 MF C20 H24 Br F2 N5 O3 S . C7 H8 O3 S
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER

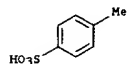
CH 1

CRN 252003-65-9
 CMF C20 H24 Br F2 N5 O3 S



CH 2

CRN 104-15-4
 CMF C7 H8 O3 S

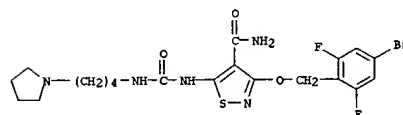


1 REFERENCES IN FILE CA (1962 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L2 ANSWER 4 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 433978-99-5 REGISTRY
 CN 4-isothiazolecarboxamide,
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monoacetate (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(4-bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-
 yl)butyl]ureido]isothiazole-4-carboxylic acid amide acetate
 MF C20 H24 Br F2 N5 O3 S . C2 H4 O2
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER

CH 1

CRN 252003-65-9
 CMF C20 H24 Br F2 N5 O3 S



CH 2

CRN 64-19-7
 CMF C2 H4 O2

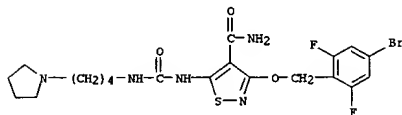


1 REFERENCES IN FILE CA (1962 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L2 ANSWER 5 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 433978-98-4 REGISTRY
 CN 4-Isothiazolecarboxamide,
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, 2-hydroxy-1,2,3-propanetricarboxylate (2:1) (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(4-Bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-yl)butyl]ureido]isothiazole-4-carboxylic acid amide hemicitrate
 MF C20 H24 Br F2 N5 O3 S . 1/2 C6 H8 O7
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER

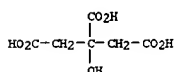
CH 1

CRN 252003-65-9
 CMF C20 H24 Br F2 N5 O3 S



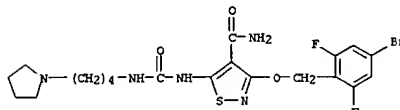
CH 2

CRN 77-92-9
 CMF C6 H8 O7



1 REFERENCES IN FILE CA (1962 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

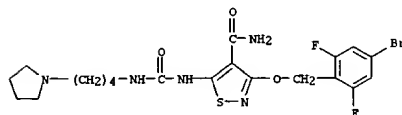
L2 ANSWER 6 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 433978-97-3 REGISTRY
 CN 4-Isouthiazolecarboxamide,
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monohydrobromide (9CI)
 (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(4-Bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-yl)butyl]ureido]isothiazole-4-carboxylic acid amide hydrobromide (1:1)
 MF C20 H24 Br F2 N5 O3 S . Br H
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER
 CRN (252003-65-9)



● HBr

1 REFERENCES IN FILE CA (1962 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L2 ANSWER 7 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 252003-71-7 REGISTRY
 CN 4-Isouthiazolecarboxamide,
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monohydrochloride (9CI)
 (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(4-Bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-yl)butyl]ureido]isothiazole-4-carboxylic acid amide hydrochloride (1:1)
 MF C20 H24 Br F2 N5 O3 S . Cl H
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
 CRN (252003-65-9)



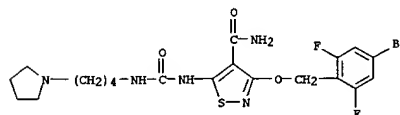
● HCl

2 REFERENCES IN FILE CA (1962 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L2 ANSWER 8 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 252003-66-0 REGISTRY
 CN 4-Isouthiazolecarboxamide,
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monomethanesulfonate (9CI)
 (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(4-Bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-yl)butyl]ureido]isothiazole-4-carboxylic acid amide mesylate
 MF C20 H24 Br F2 N5 O3 S . C H4 O3 S
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CH 1

CRN 252003-65-9
 CMF C20 H24 Br F2 N5 O3 S



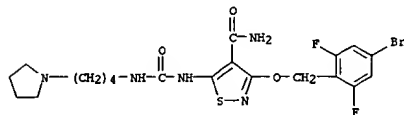
CH 2

CRN 75-75-2
 CMF C H4 O3 S



2 REFERENCES IN FILE CA (1962 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

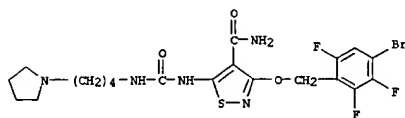
L2 ANSWER 9 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 252003-65-9 REGISTRY
 CN 4-Isothiazolecarboxamide,
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[(4-
 (1-pyrrolidinyl)butyl)amino]carbonyl]amino]- (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN 3-[(4-bromo-2,6-difluorobenzyl)oxy]-5-[3-[4-(pyrrolidin-1-
 yl)butyl]ureido]isothiazole-4-carboxylic acid amide
 FS 3D CONCORD
 MF C20 H24 Br F2 N5 O3 S
 CI COM
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L2 ANSWER 10 OF 10 REGISTRY COPYRIGHT 2002 ACS
 RN 252003-63-7 REGISTRY
 CN 4-Isouthiazolecarboxamide,
 3-[(4-bromo-2,3,6-trifluorophenyl)methoxy]-5-
 [[[(4-(1-pyrrolidinyl)butyl)amino]carbonyl]amino]- (9CI) (CA INDEX
 NAME)
 FS 3D CONCORD
 MF C20 H23 Br F3 N5 O3 S
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> FILE REG

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	156.46	156.67

FILE 'REGISTRY' ENTERED AT 17:35:04 ON 20 SEP 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file .
provided by InfoChem.

STRUCTURE FILE UPDATES: 19 SEP 2002 HIGHEST RN 453507-55-6
DICTIONARY FILE UPDATES: 19 SEP 2002 HIGHEST RN 453507-55-6

TSKA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP
PROPERTIES for more information. See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> STR 252003-65-9

:END

L3 STRUCTURE CREATED

=> S L3 FAM FUL

FULL SEARCH INITIATED 17:35:07 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 19 TO ITERATE

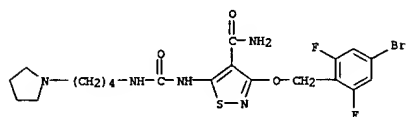
100.0% PROCESSED 19 ITERATIONS 9 ANSWERS
SEARCH TIME: 00.00.01

L4 9 SEA FAM FUL L3

=>

=> D SCAN

L4 9 ANSWERS REGISTRY COPYRIGHT 2002 ACS
 IN 4-Isothiazolecarboxamide,
 3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-, monohydrochloride (9CI)
 MF C20 H24 Br F2 N5 O3 S . Cl H



● HCl

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> s 14 and caplus/lc
24550097 CAPLUS/LC
L5 9 L4 AND CAPLUS/LC

=> fil caplus	SINCE FILE	TOTAL
COST IN U.S. DOLLARS	ENTRY	SESSION
FULL ESTIMATED COST	58.98	215.65

FILE 'CAPLUS' ENTERED AT 17:35:24 ON 20 SEP 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 20 Sep 2002 VOL 137 ISS 13
FILE LAST UPDATED: 19 Sep 2002 (20020919/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s 15
L6 2 L5

=> d 1-2 ibib abs hitstr

SALTS OF A ISOTHIAZOLE-4-CARBOXAMIDE AND THEIR USE AS ANTI-HYPERPROLIFERATION AGENTS

Patent Number: WO0244158
Publication date: 2002-06-06
Inventor(s): WILLIAMS GLENN ROBERT (US); GANT THOMAS G (US)
Applicant(s): WILLIAMS GLENN ROBERT (US); GANT THOMAS G (US); PFIZER PROD INC (US)
Requested Patent: ☐ WO0244158
Application Number: WO2001IB02193 20011119
Priority Number(s): US20000253513P 20001128
IPC Classification: C07D275/03; A61K31/427; A61P35/00
EC Classification: C07D275/02D3
Equivalents:
Cited Documents: WO9962890

Abstract

The invention relates to hydrochloride, hydrobromide, hemi-citrate, acetate, p-tosylate, L-tartrate, hemi-succinate, and mesylate salt forms of 3-(4-bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide having the following formula: formula 1. The invention also relates to pharmaceutical compositions containing the hydrochloride, hydrobromide, hemi-citrate, acetate, p-tosylate, L-tartrate, hemi-succinate, and mesylate salts of formula 1. The invention further relates to methods of treating hyperproliferative diseases, such as cancers, in mammals, especially humans by administering the above salts and to methods of preparing the crystal forms of the above salts.

Data supplied from the esp@cenet database - I2

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/IB 01/02193

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D275/03 A61K31/427 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 62890 A (PFIZER PRODUCTS INC.) 9 December 1999 (1999-12-09) the whole document, particularly page 13, lines 1-12, and claim 9, 1st and 8th compound -----	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

28 February 2002

Date of mailing of the international search report

06/03/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Allard, M

INTERNATIONAL SEARCH REPORT
Information on patent family members

In International Application No
PCT/IB 01/02193

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9962890	A	09-12-1999	AU 3342199 A 20-12-1999
		BG 104998 A 31-07-2001	
		BR 9910900 A 13-02-2001	
		CN 1303380 T 11-07-2001	
		EP 1084114 A1 21-03-2001	
		HR 20000835 A1 31-12-2001	
		WO 9962890 A1 09-12-1999	
		NO 20006071 A 30-11-2000	
		PL 344691 A1 19-11-2001	
		US 6235764 B1 22-05-2001	
		US 2001020034 A1 06-09-2001	
		ZA 9903752 A 04-12-2000	
